REMARKS

Applicants thank the Examiner for withdrawing all previous rejections of the claims.

Applicants thank the Examiner for the indicated allowance of claims 2, 6, 10 and 21.

The Examiner has rejected claims 1, 3, 4, 7, 11, 12, 20 and 22-29 under 35 U.S.C. 102(b) as being anticipated by US 6,440,677, claiming priority to March 10, 1997.

The Examiner argues:

> Lipschutz et al. teach amplifying a multiplicity of oligonucleotides to provide a pool of amplified nucleic acids and attaching the pool of nucleic acids to a solid support. In particular, Lipschutz et al. teach that nucleic acids can comprise of a first priming domain and then a second priming domain and then a "unique" domain and a second priming domain, which would encompass the limitations set forth in claim number 1 which requires a first string of universal nucleotides and a first segment followed by a second string and a second segment (see Figure 1 template and column 16, lines 5-14). Because the claim does not specifically state the universal nucleotide(s) of preference, the arrangement of Lipschutz et al. anticipate the claim. Furthermore, Lipschutz et al. go on to detail that oligonucleotide analogues may be utilized in the invention and therefore, claims 4, 7, 8, 11, 12, 20 and 22-29, which include "and/or analogues", are anticipated (see column 18, lines 25-30). Finally, recognition sequences can be placed on the ends, as in claim 3 (column 16, lines 23-38).

As a preliminary matter, Applicants respectfully note that the cited patent was not published until August 27, 2002, which is after the filing date of the present application. Accordingly, the 6,440,677 patent is not prior art under 35 U.S.C. 102(b). At best, the cited patent could possibly be prior art under 35 U.S.C. 102(e), as it claims priority to March 10, 1997. Applicants believe that this point is moot in view of the arguments presented below, demonstrating the general inapplicability of this reference to the claims in question. Nonetheless, should these arguments be considered unpersuasive, Applicants reserve the right to establish that the 6,440,677 patent is not prior art by, for example, establishing a prior date of invention.

Applicants respectfully disagree with the Examiner's characterization of the 6,440,677 patent as anticipating the any of the claims of the present application. It is axiomatic that in

order to anticipate a claim, a reference must disclose each an every element of the claimed subject matter, either explicitly or inherently.

*The Present Claims, and "Universal Nucleotide"*

Each of the present claims at issue comprises "a first string of universal nucleotides...and a second string of universal nucleotides". As understood in the specification and in the now-extensive prosecution record, the term universal refers to: "an entity (or collection of entities mutually substituted at a position) that is relatively non-specific with respect to all of A, T, C and G. Exemplary universal bases are 5-nitroindole and 3-nitropyrrole. As would be appreciated by one of skill in the art, any 'universal' base will have some heterogeneity in free energy of hybridization with different partners." (see Applicants' response dated Aug. 3, 2001).

*The 6,440,677 Patent*

Taking the definition above, the '677 patent does not teach, suggest or imply any use of a "universal nucleotide" in the disclosed probes. Furthermore, the '677 patent does not (and could not possibly) teach, suggest or imply any patterning of universal nucleotides. The Examiner has pointed to Figure 1, which shows an polynucleotide consisting of a 5'-primer region (primer B), a central probe region, a 3'-primer region (primer A) and a 3' cleavable linker. The Examiner has also pointed to column 16, lines 5-14, which recites a similar type of polynucleotide. Below, we show that there is no teaching for the use of a universal nucleotide in any of these regions of the probes disclosed in the '677 patent, and furthermore, the '677 patent teaches against the use of such probes.

The '677 patent does not suggest that the central probe region should contain a universal nucleotide. As described in the '677 patent, the central probe region is referred to as the "unique" region, meaning that this probe is intended to hybridize to a single species of nucleic acid in a pool of nucleic acids. At column 12, lines 9-39, the patent describes criteria for selecting the probe nucleic acids that are needed. The document states (lines 35-39) that these criteria are important because "otherwise the probes comprising the affinity matrix will be unable to specifically discriminate between target nucleic acids and non-target nucleic acids having similar, but not identical, sequences." The stated purpose of the central probe region is,

therefore, specific interaction with target nucleic acids. This purpose, as would be understood in the art, is inconsistent with the use universal nucleotides which would tend to decrease the specificity of the probe. Therefore, not only does the '677 patent fail to teach the use of a universal nucleotide in the central probe, it also teaches away from such use.

The '677 patent does not suggest the use of universal nucleotides in the primer regions of the probes. At column 16, lines 5-14, the '677 patent merely indicates that the primer regions may have different or identical sequences. There is no mention of a universal nucleotide. At column 16, lines 20-22, the patent reads "Priming domains are preferably selected so that the priming domain does not also form a subsequence in any of the unique regions of the templates." One of ordinary skill in the art would understand that the use of universal nucleotides would increase the likelihood that a priming domain would hybridize with a unique region (central probe region) of the probes. Therefore, not only does the '677 patent fail to teach the use of a universal nucleotide in the priming regions of the probes, it also teaches away from such use.

Applicants were unable to identify any description of the "cleavable linker" portion of the '677 probes. In the absence of any teaching whatsoever, the term "cleavable linker" cannot properly be construed as describing universal nucleotides. In fact, it would seem unlikely that a universal nucleotide would be susceptible to cleavage by most enzymatic cleavage reagents.

Surprisingly, the Examiner does not attempt to argue that there is any teaching of a universal nucleotide in the '677 patent. Instead, the Examiner attempts to sidestep this lack of teaching in the '677 patent by asserting that a precise universal nucleotide is not specified in the present rejected claims, and that therefore, one of the probes of the '677 patent might possibly contain universal nucleotides arranged in a pattern so as to meet the elements of the present claims. Given that the '677 patent does not teach or suggest the use of any nucleotide or mixture thereof that would come within the definition of "universal nucleotide" that has been established in this prosecution, the Examiner can only have reached this conclusion by interpreting the term "universal nucleotide" as encompassing any of the naturally occurring or otherwise designate nucleotides disclosed in the '677 patent. Yet, the Examiner may not construe a claim term in such a plainly incorrect manner and in a manner plainly contradictory to the meaning in the art; claim terms are to be interpreted in light of the specification, the prosecution history and, as a

less persuasive authority, the general knowledge in the art. The specification and prosecution history have plainly established a meaning for the term "universal nucleotide", recited above. The previous Examiner in this case (Examiner Zeman) has, herself, stated that "universal nucleotides are able to bind to any natural nucleotide in a sequence. (See p.4, Office Action March 11, 2002). The Examiners have cited references such as Mirzabekov (US 5,681,947) which recites numerous examples of universal bases and even provides a definition of the term "universal base" which, although somewhat different than that used herein, clearly shows an understanding in the art that "universal" as used in reference to nucleotides is not a meaningless term. Furthermore, the present disclosure broadly describes a sequencing by hybridization system that is plainly effective without regard to the specific universal nucleotide that is selected. The calculations presented in the examples are generic with respect to the precise universal nucleotide that is selected.

Accordingly, Applicants assert that it is incorrect, as a matter of claim interpretation, to read the term "universal nucleotide" so broadly as to encompass the single, designate unmixed bases, such as A, T, C, or G, that are taught in the '677 patent. Furthermore, such interpretation is a marked departure from the meaning of "universal nucleotide" that both Applicants and two different Examiners have followed and explicitly discussed through two years of prosecution, at least four office actions, several telephonic interviews and innumerable prior art rejections. Applicants have prosecuted these claims in good faith and always with a goal of advancing prosecution. It is unfair and unreasonable at this late stage of prosecution to return to this rudimentary point and to produce a reference of such limited relevance as the '677 patent, which could have been cited at the outset of prosecution.

Applicants earnestly entreat the Examiner to allow the pending claims. In view of the exceptionally high level of review that the present claims have been subject to, and the deteriorating relevance of the recently cited art, Applicants state with great confidence that the present claims are patentable and should be allowed.

Applicant believes no fee is due with this response other than the accompanying fee for a one month extension of time. However, if a fee is due, please charge our Deposit Account No. 18-1945, under Order No. BURF-P01-010 from which the undersigned is authorized to draw.

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Respectfully submitted,

By _____

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